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Review

Now and future: Strategies for diagnosis, prevention and therapies for Alzheimer's disease

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ABSTRACT

After a number of failed drug studies on Alzheimer's disease (AD) over the past decade, clinical trials of AD started to show encouraging results and were approved or pending approval for clinical use. However, controversies on the clinically meaningful benefits and risks of brain edema and microhemorrhages have reminded us to think further about monitoring treatment and developing new drug targets. The goal of this review is to find insights from clinical trials that aimed at two key pathological features of AD, i.e., amyloid-β (Aβ) and tau protein, and to explore other targets such as anti-inflammation in AD. The complex pathophysiology of AD may require combination therapies rather than monotherapy. Throughout the course of AD, multiple pathways are disrupted, presenting a multitude of possible therapeutic targets for designing prevention and intervention for AD.

Alzheimer's disease (AD) is a neurological disorder with the characteristic progressive and irreversible decline in memory and other cognitive functions. It is the most common form of dementia that causes loss of cognition and independence of living among older people. Early diagnosis and early treatment are crucial in the management of AD. The goal of this article is to provide a comprehensive analysis of the current state of AD and future directions. It focuses on key aspects that are crucial for both clinicians and researchers. In this review, we first examined the global epidemiological features of AD to gauge its prevalence and distribution across different regions and populations. We then delve into the latest advancements in diagnostic biomarkers, emphasizing innovative approaches that hold promise for earlier and more accurate detection of the disease. A significant portion of our discussion centers on emerging therapeutic strategies. We evaluate the progress in anti-amyloid and anti-tau therapies, as well as novel treatments targeting alternative pathological mechanisms. Furthermore, we investigate the potential of combination therapies and personalized medicine approaches in managing this complex disease. Additionally, we address the critical role of governmental and social investments in AD research and care. By examining these interconnected aspects, from epidemiology to diagnosis, treatment, and health initiatives and policies, we help to shed light on future treatment and management of AD.

1. AD epidemiology

About 50 million people worldwide have dementia, and there are nearly 10 million new cases every year. The switch from normal aging to a chronic disease state is an early development in the process of age-related diseases. To address this critical issue, the international community has adopted a strategy with a primary focus on monitoring and preventing age-related diseases.

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The prevalence and incidence of AD and other related dementia (ADRD) are projected to rise in the future due to the age-related escalation in dementia risk. About 66.7% of people with dementia live in countries with low- and middle-income [1]. About 10.8% of people aged 65 years and older have AD in the USA [2]. In China, the number of people with dementia is more than 15.1 million. In individuals aged 60 years and above in China, the prevalence of dementia is 6%. AD is the most prevalent form, accounting for 65% of all dementia cases. AD has become a heavy health and economic burden [3]. An analysis was conducted to compare the prevalence, mortality rates, healthcare costs, and government policies related to ADRD in China with those in Japan, the USA, Europe, and globally (Table 1) [3–11].

2. AD diagnosis

Early and precise diagnosis of AD facilitates disease monitoring and treatment [12]. The criteria for AD diagnosis has been evolving into several stages: The first stage was when the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) issued the diagnostic criteria first in July 1984 [13]. The diagnostic criteria included two parts: the diagnostic criteria for dementia and the diagnostic criteria for AD, which were further classified into possible AD, probable AD and definite AD [13].

Since this criterion is not specific for the diagnosis of non-AD dementia cases, in the second stage, the International Working Group (IWG) proposed the concept of mild cognitive impairment (MCI) for the first time in 2007. It classified AD into MCI, prodromal AD and AD dementia [14]. The IWG diagnostic criteria for AD included biomarkers to help make a diagnosis. The National Institute on Aging and Alzheimer's Association (NIA-AA) issued the diagnostic criteria in 2011 to emphasize the importance of biomarkers, especially when making the diagnosis of preclinical AD [15]. As advances in the development of biomarkers, the third stage came when NIA-AA proposed a research framework for AD in 2018. It brought the spectrum of AD with different stages and phenotypes with the same biomarkers into the same research framework, that is, the A-T-N research framework. It provides a basis for exploring the biological heterogeneity of AD. The A-T-N research framework emphasized the importance of biomarkers of amyloid-β (Aβ) plaques (A, measured by amyloid positron emission tomography (PET) imaging or low cerebrospinal fluid (CSF) Aβ42), fibrillary tau (T, as determined by tau PET imaging or increased CSF phosphorylated tau, and signs of neurodegeneration (N, measured by CSF total tau (tTau), fluorodeoxyglucose (FDG)-PET showing cerebral metabolic reduction, and cortical atrophy on magnetic resonance imaging (MRI)) in the process of AD [16]. Multiple studies have shown that the combination of tau and Aβ positivity was insufficient to accurately predict the onset of symptoms in individuals without clinical impairment [17–19]. Therefore, in 2021, the IWG advised that the diagnosis of AD should be based on a combination of clinical and biological evidence. It necessitates the presence of a distinct clinical phenotype indicative of AD (phenotype-positive) alongside biomarker evidence demonstrating AD pathology (amyloid-positive and tau-positive). The specific clinical phenotypes commonly linked to AD pathology, known as common AD phenotypes, include the amnestic syndrome of the hippocampal type (typical), the logopenic variant primary progressive aphasia, and the posterior cortical atrophy variant. The diagnostic criteria of AD have gradually evolved in clinical practice and research as our understanding of the disease advances.

Therefore, it is crucial to identify effective biomarkers to achieve early diagnosis when patients only have subtle symptoms. However, the effective measurement of biomarkers is influenced

Table 1
Information of AD or other dementias in China compared to Japan, Europe, USA and the globe.

	China (2019)	Japan (2019)	European (2019)	USA (2021)	The Globe (2019)
AD or other dementias population (million)	15.1 (14.5–15.6)	4.1 (3.5–4.8)	8.9	5.3 (4.7–5.7)	57.4 (50.4–65.1)
AD or other dementias prevalence	6.2% (≥60 years old)	11.3% (≥65 years old)	1.73% (population)	10.7% (≥65 years old)	5.5%–7.0% (≥60 years old)
Deaths due to dementia in 2019 (million)	0.33	0.16	0.39	0.14	1.62
National cost for individuals with AD or other dementias per year (billion US dollars)	248	119 (AD)	300	321	1330
Major national dementia policies and healthcare system	National dementia plan was enacted in 2020; National Health Commission released the Prevention and Treatment Guide for AD to educate the public on active prevention of AD in 2019; Chinese NSFC, CAS and MOST have funded research on dementia.	National dementia plan in 2012; Japanese government has enacted public health campaigns to facilitate early action on dementia in 2005; Japan's National Center for Geriatrics and Gerontology has led a number of studies on dementia prevention and risk reduction.	European Alzheimer's Alliance was launched in 2007; the Alliance Released several strategic plans to strengthen the European dementia movement and support dementia research.	National plan on AD in 2011 with the National Alzheimer's Project Act in 2011; the US federal government promotes prevention and early detection through both direct public resources and partnerships with advocacy organizations, state public health agencies, and local communities.	N/A

Modified from Ref. [1] AD, Alzheimer's disease; NSFC, National Natural Science Foundation of China; CAS, Chinese Academy of Science; MOST, Ministry of Science and Technology; N/A, not applicable.

by race, environmental factors, etc. Research conducted on Caucasian populations has recognized several plasma molecules, such as Aβ42, Aβ40, pTau 181, and pTau 217, as key biomarkers for AD [20,21]. These core AD biomarkers have been shown to accurately distinguish AD dementia from non-AD dementia. More recent studies have involved Chinese populations [22–24]. A multicenter longitudinal study analyzed 817 blood samples from individuals with AD, cerebral amyloid angiopathy, cerebral small vessel disease, and cognitively normal elderly individuals. The study identified pTau 181 and glial fibrillary acidic protein (GFAP) as robust predictors of cerebral amyloid deposition [25]. A clinical study in Shanghai, China described the profile of blood-based biomarkers, including plasma Aβ40, Aβ42, tTau, phosphorylated tau (pTau) 181 and serum neurofilament light (NfL). It demonstrated that pTau181 in the plasma is the most reliable biomarker for Chinese individuals with AD [26,27]. A different study conducted in Hefei, China assessed plasma BACE1 activity in subjects with AD, MCI, and healthy controls. The findings revealed that BACE1 levels were significantly elevated in both AD patients and MCI converters. These results suggest that plasma BACE1 activity could serve as a biomarker for the risk of developing AD [28]. An exploratory study sought to identify naturally occurring antibodies to Aβ (NAbs-Aβ) in AD [29]. The study proposed that alterations in the epitope-specific profile of NAbs-Aβ in individuals with preclinical and clinical AD could serve as a promising biomarker for AD. Additionally, a study conducted in Hong Kong, China established a 19-protein biomarker panel tailored for distinct stages of AD [30]. The study showcased that a combined biomarker panel has the potential for precise diagnosis of AD.

The combination of biomarkers and advanced technology assessment tools helps to streamline the diagnostic process. The Ace Alzheimer Center Barcelona in Spain has conducted a comprehensive analysis, correlating CSF biomarkers and MRI with a cutting-edge, computerized, self-administered verbal episodic memory test featuring voice recognition (FACEmemory®). This innovative approach aims to identify memory deficits associated with underlying AD and to distinguish memory-impaired cases from other etiologies. This new technique may help to expedite the detection of early MCI cases [31].

Synaptic damage occurs in the pre-symptomatic stage of AD, so it is feasible to use synaptic proteins as biomarkers for AD [32]. Exosomes have garnered significant attention as a means to characterize diverse phenotypes from clinical, neuropsychological, and biomarker perspectives. A two-stage cross-sectional study showed that individuals with AD or preclinical AD displayed reduced levels of various synaptic proteins, such as synaptosome-associated protein 25 (SNAP25), growth-associated protein 43 (GAP43), synaptotagmin, and neurogranin, in neuronal-derived exosomes [33]. These plasma exosomes exhibit a strong correlation with those present in CSF and demonstrate a high efficacy in detecting AD during the asymptomatic stage.

A recent study conducted at six tertiary clinical centers in China examined 817 blood samples in both cross-sectional and longitudinal analyses [25]. It measured plasma Aβ40, Aβ42, pTau 181, tTau, serum NFL and GFAP, and correlated the plasma results with that of ^{18}F-florbetapir PET and MRI. It demonstrated that a combination of the *APOE* genotype with plasma pTau and serum GFAP has the best value in distinguishing Aβ status. Furthermore, The initial levels of GFAP showed a robust correlation with cognitive deterioration and brain volume loss over time, indicating that elevated GFAP levels were indicative of a faster pace of neurodegeneration. These results validate the usefulness of blood biomarkers in China across different regions. Furthermore, they underscore the promise of pTau and GFAP as non-invasive approaches for the early detection or screening of AD. It's worth noting that the level of pTau is different from that of the Caucasian population. A head-to-head comparison study of populations with different races is warranted.

AD is a neurodegenerative disease. The treatment of AD is used to focus on relieving the symptoms of the disease. It has two classes of drugs. One is cholinesterase inhibitors for mild to moderate AD, including tacrine, donepezil, rivastigmine and galantamine. The tacrine was discontinued due to its liver toxicity. The other is an NMDA receptor modulator, memantine, which is for moderate to severe AD. With a better understanding of the pathogenesis of AD, disease-modifying therapy (DMT) started to emerge to address the underlying cause. The key pathological features of AD include amyloid plaques and tau protein neurofibrillary tangles, making them the primary target for pharmaceutical research in AD (Fig. 1).

3. AD treatment

3.1. Anti-Aβ drugs

The failure of previous study drugs (bapineuzumab, crenezumab, solanezumab, semagacestat, verubecestat) targeting against different forms Aβ or its critical enzymes (γ- or β-secretase) may be related to a delay in starting the treatment and/or poor blood–brain barrier (BBB) permeability to the brain [34,35]. A reduction in peripheral free Aβ alone is not sufficient to reduce deposited cerebral amyloid that is involved in pathological cascades leading to dementia. The amount of the anti-Aβ antibodies entering the brain may be not enough to stimulate microglial cells to neutralize Aβ in the brain to produce a clinically meaningful effect [36]. In addition to BBB permeability, the Aβ load has to be lowered below a threshold to produce a clinical benefit. The gantenerumab, another anti-amyloid antibody, failed to slow cognitive decline in two phase 3 GRADUATE trials. The treatment achieved only a partial reduction in Aβ plaques, with fewer participants achieving amyloid negativity on PET scans compared to prior studies. Although clinical measures showed some improvement, they did not reach statistical significance [37]. There is little correlation between Aβ deposition and the progression of cognitive impairment, but tau neurofibrillary tangles are associated with the disease progression [34]. Therefore, only when soluble Aβ is decreased to a non-pathogenic level, that is, a level that cannot

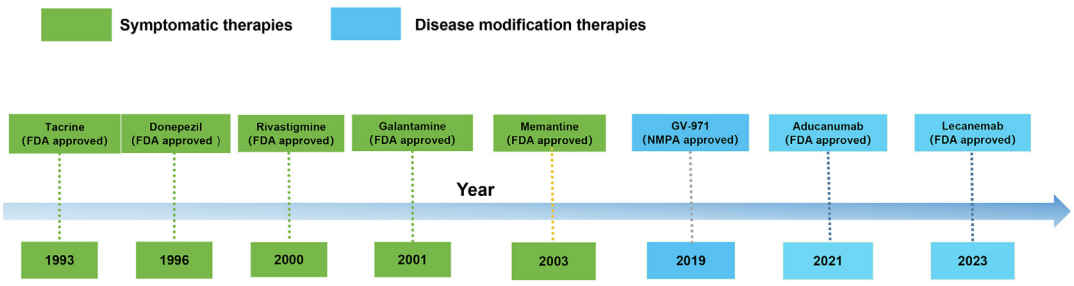

Fig. 1. Summary of drug therapies for AD. Aβ, amyloid-β; FDA, the US Food and Drug Administration; NMPA, National Medical Products Administration.

cause the formation of tau pathology, may clinical benefits be achieved [34].

Aducanumab, an antibody binding to aggregated forms of Aβ, not to the monomer Aβ was the first anti-Aβ antibody approved by the US Food and Drug Administration (FDA) on June 7, 2021. In the ENGAGE trail, aducanumab did not reduce the cognitive decline in primary endpoints. But in the parallel EMERGE trail, aducanumab in the high-dose group reduced the cognitive decline and reached the primary and secondary endpoints. EMERGE was the inaugural trial to demonstrate the significant impact of an anti-amyloid drug on cognitive decline in individuals with MCI and early AD [38].

Lecanemab is a humanized IgG1 monoclonal antibody that targets at Aβ soluble protofibrils. It reduces amyloid levels in early AD and leads to less cognitive and functional decline at 18 months in a multicenter, double-blind, phase 3 trial [39]. The US FDA granted accelerated approval to lecanemab in January 2023. A US FDA advisory panel unanimously supported its clinical benefits for treating the disease, setting the stage for the full US FDA approval in July 2023.

Donanemab, a humanized IgG1 antibody that specifically targets the pyroglutamate form of aggregated Aβ found in amyloid plaques, has been reported to reduce clinical decline by 35% compared to a placebo. Additionally, it led to a 40% decrease in the decline of daily living activities among participants in the study. The phase 3 study of TRAILBLAZER-ALZ 2 met the primary endpoint and all secondary endpoints [40]. The scientific advisory board for the US FDA voted unanimously for lecanemab in June 2024. US FDA granted it the full approval a month later.

SHR-1707, a humanized anti-amyloid monoclonal antibody, was designed to prevent the assembly of β-amyloid plaques by activating microglial phagocytosis of various forms of Aβ. A randomized, double-blind, placebo-controlled, phase II study of SHR-1707 was designed to recruit AD patients in China (NCT 05681819) [41].

The administration methods and therapeutic dosages from previous antibody studies are summarized in Table 2. All anti-amyloid monoclonal antibodies have notable adverse events of amyloid-related imaging abnormalities (ARIA) which are usually asymptomatic and rarely cause severe symptoms. Although its etiology is unclear, it seems to be dose- and ApoE4-dependent. It is recommended to have clinical and neuroimaging monitoring [42].

3.2. Anti-tau drugs

Tau tangles are closely related both spatially and temporally to the onset and progression of neurodegeneration. In addition to reducing different forms of Aβ, anti-Aβ antibodies also reduce tau protein in the brain. Treatment with aducanumab leads to substantial decreases in plasma pTau181 in a dosage- and time-dependent fashion when compared to a placebo [43]. Findings from a tau PET sub-study of 36 patients demonstrated a reduction in tau tracer uptake in the medial temporal lobe, indicating a potential reduction in tau tangle pathology after aducanumab treatment. [2] Lecanemab not only directly removes amyloid plaques but also has downstream effects on tau pathology. Studies on tau biomarkers showed that amyloid clearance led to improvements in CSF and plasma levels of pTau (pTau181), which are downstream markers in the AD pathology pathway. Additionally, tau PET analysis revealed that lecanemab treatment decelerated tau accumulation in the temporal lobe and enhanced total tau levels compared to the placebo group [39]. Donanemab treatment reduces both Aβ and tau in the brains of people [44]. Data also showed that treatment with donanemab drove a rapid reduction of plasma pTau217, which was detected within 12 weeks after the treatment [45].

Anti-tau antibodies are emerging to become a new way to treat AD [46]. Progressive supranuclear palsy (PSP) is a rare neurodegenerative disease that is considered a primary tauopathy. However, anti-tau antibodies such as gosuranemab (a humanized IgG4 monoclonal anti-tau antibody) and tilavonemab (a humanized IgG4 antibody) failed to achieve the expected results in phase 2 clinical trials of PSP and AD (Table 3) [47–49]. In addition to monoclonal antibody immunotherapies, a number of small molecule drugs and DNA/RNA-based drugs targeting tau protein are being investigated. TPI287 is a drug based on tubulin binding and enhances microtubule stabilization [50]. As a synthetic derivative of taxane diterpenoids, TPI287 differs from most taxanes in its ability to cross the BBB and enter the brain to produce its therapeutic effects. It's shown to improve cognitive function in a small phase 2a trial. However, the TPI287 study showed no differences in CSF biomarker endpoints between treatment and placebo groups in AD patients. The activation of autophagy by sigma-1 receptors (σ-1Rs) in combination with other neuroprotective effects presents a compelling target for AD treatment [51]. Blarcamesine, a σ1 muscarinic ligand, can bind to muscarinic acetylcholine and σ1 receptors to reduce glycogen synthase kinase-3β (GSK3-β) activity and to prevent tau hyperphosphorylation. It may help to improve memory loss and have neuroprotective effects [52]. BIIB080, the first antisense oligonucleotide (ASO) targeting tau expression in mild AD, was reported in a phase 1b, randomized, placebo-controlled trial. It showed that in the two treatment groups that received the highest dose of antisense oligonucleotides (60 and 115 mg), tTau levels and pTau levels were reduced by more than 50% in the central nervous system after 24 weeks [53]. These studies suggest that drugs targeting tau protein at the pathological level may improve the pathological progression of AD, but there is still a lack of evidence for clinical benefits.

3.3. Drugs on other targets

Inflammation plays a crucial role in AD, as well as in cerebrovascular disease and aging. Studies have investigated the impact of inflammation on AD, with markers like C-reactive

Table 2
Drugs target Aβ in Alzheimer's disease.

Anti-Aβ antibody	Company	Origin type	IgG class	Aβ epitopes	Aβ monomeric	Aβ oligomers	Aβ fibrillar	Administration route	Dose regimen
Bapineuzumab	Janssen/Pfizer	Humanized	IgG1	AA 1–5	Y	Y	Y	iv	0.15, 0.5, 1, 2 mg/kg
Aducanumab	Biogen	Fully human	IgG1	AA 3–6	N	Y	Y	iv	10 mg/kg
Lecanemab	Biogen/Eisai	Humanized	IgG1	Protofibrils	N	N	Y	iv	10 mg/kg
Donanemab	Eli Lilly	Humanized	IgG1	Aβ (p3–42)	N	N	Y	iv	700 to 1400 mg
Solanezumab	Eli Lilly	Humanized	IgG1	AA 16–26	Y	N	N	iv	400 to 1600 mg
Gantenerumab	Roche	Fully human	IgG1	AA 3–12; 18–27	N	Y	Y	sc	1200 mg
Crenezumab	Roche	Humanized	IgG4	AA 13–24	Y	Y	Y	sc	6800 mg
Ponezumab	Pfizer	Humanized	IgG1	AA 3–6	N	Y	Y	iv	10 mg/kg

iv, intravenous injection; sc, subcutaneous injection.Y, yes; N, no.

Table 3
Drugs target tau protein in Alzheimer's disease.

Tau-related	Company	Therapy type	Target	US FDA status	Administration route	Dose regimen
Gosuranemab	Biogen/Bristol-Myers Squibb	Immunotherapy (passive)	Anti-tau antibody IgG4	Discontinued	iv	50 mg/mL
Tilavonemab	AbbVie, C2N Diagnostics, LLC	Immunotherapy (passive)	Anti-tau antibody IgG4	Discontinued	iv	300, 1000 or 2000 mg
Semorinemab	AC Immune SA, Genentech, Hoffmann-La Roche	Immunotherapy (passive)	Anti-tau antibody IgG4	Phase 2	iv	1500, 4500, or 8100 mg
Zagotenemab	Eli Lilly	Immunotherapy (passive)	Anti-tau antibody IgG4	Discontinued	iv	1400 mg, 5600 mg
Bepranemab	Hoffmann-La Roche, UCB S.A.	Immunotherapy (passive)	Anti-tau antibody IgG4	Phase 2	iv	NA
Blarcamesine	Anavex Life Science Corp.	Small molecule	σ1 receptor	Phase 2/3	po or iv	20 or 30 mg
TPI287	Cortice Biosciences	Small molecule	Tubulin-binding	Inactive	iv	2, 6.3, 20 mg/m^2
BIIB080	Biogen/IONIS	DNA/RNA-based	Tau expression	Phase 1	it	NA

iv, intravenous injection; sc, subcutaneous injection; it, intrathecal injection; NA, Not available; po, *per os*.

protein and interleukin-6 (IL-6) being linked to neuronal and synaptic loss, as well as impaired cognitive function in the elderly. Chronic brain inflammation is another AD pathology. Therefore, treatments of anti-Aβ antibodies also have effects on inflammation in the central nervous system. Although the changes of inflammatory factors in the brain of patients after aducanumab treatment were not reported in clinical trials, aducanumab-treated primary microglia *in vivo* exhibited significantly increased levels of tumor necrosis factor (TNF), IL-6, and IL-1β [54]. In the lecanemab phase 3 trial, both a CSF sub-study and the plasma analysis of the entire study population showed a pronounced reduction in levels of GFAP after lecanemab treatment [39]. In the donanemab trial, the plasma levels of GFAP were decreased by 12% from baseline after treatment, whereas it was increased by 15% in the placebo group [55].

Despite efforts to utilize anti-inflammatory treatments such as low-dose aspirin, low-dose prednisone, selective cyclooxygenase-2 inhibitors, non-steroidal anti-inflammatory drugs, and etanercept, these interventions have not demonstrated efficacy in AD patients. Drugs targeting inflammatory factors, such as IL-1β inhibitor (canakinumab, NCT04795466) and soluble TNF inhibitor (XPro1595, NCT03943264) are also in the study of phase 1b and 2 clinical trials (Table 4) [56,57]. The emerging role of microglial and astroglia activation for AD pathogenesis makes these cells a legitimate therapeutic target. The compound AD16, an inhibitor of neuronal inflammation, was reported to reduce Aβ plaques and to modify microglia in a transgenic mouse model of AD. Mice treated for AD16 showed decreased activation of microglia, amyloid plaque accumulation, and surrounding gliosis. Clinical phase 2 trials are on the way [58]. Studies have shown that a small G protein Rac-dependent mechanism plays a role in passive memory decay and interference-induced forgetting in *Drosophila* [59]. Inhibiting the excessive activation of Rac1 protein in AD patients is proposed to help AD patients with their memory impairment. JK-50561 is the first drug to treat amnesia (first in concept) and is currently in phase 2 clinical trials (NCT05811442) [60]. GV-971, a sodium oligomannate, was reported to reach the primary endpoint of improving cognitive function in a phase 3 clinical trial. In animal models, it was demonstrated that GV-971 suppressed gut dysbiosis and the associated phenylalanine/isoleucine accumulation, reduced neuroinflammation and ameliorated cognition impairment [61]. The China National Medical Product Administration (NMPA) conditionally approved its therapy for AD, on which phase 4 clinical trials are ongoing (NCT05181475, NCT05058040, and NCT05908695) [62–64].

4. Future directions

Trials of anti-Aβ treatment have started to show encouraging results of biomarkers and more importantly clinical benefits. Regardless of the antibody targeting a variety of Aβ forms, it has to reduce amyloid below a certain threshold to achieve the primary and secondary endpoints. It suggests that anti-Aβ alone is necessary but not sufficient to have a robust clinical benefit. All three approved anti-Aβ antibodies also reduce tau protein in the brain.

Table 4
Drugs on inflammation and other targets.

Inflammation-related and other	Company	Therapy type	Target	US FDA status	Administration route	Dose regimen
Canakinumab	Novartis	Small molecule	IL-1β	Phase 2	sc	NA
XPro1595	INmune Bio Inc.	Small molecule	TNF	Phase 2	sc	1.0 mg/kg
AD16	The South China Center for Innovative Pharmaceuticals	Small molecule	Neuroinflammation	Phase 2	po	5 to 80 mg
GV-971	Shanghai Green Valley Pharmaceuticals	Small molecule	intestinal bacteria	Inactive	po	450 mg
JK-50561	Beijing Zhuokai Biotechnology	Small molecule	Rac1 protein	Phase 2	po	128 or 256 mg

sc, subcutaneous injection; po, *per os*.

The underlying pathophysiology points to multiple factors including inflammation, immunity, synaptic degeneration, and vascular factors. To borrow a page from cancer and HIV treatment, cocktail treatment with multi-target therapy may be the answer to the complex pathology of the disease. Funding and policy should at least encourage the attempt of multi-drug combination therapy. More basic research will be needed to further explore new therapeutic targets.

5. Governmental and social investment

The World Health Organization (WHO) has identified dementia as a significant public health concern. In response to dementia 2017–2025, the World Health Assembly in May 2017 endorsed the global action plan which considers dementia as a public health priority. It aims to increase awareness of dementia [65].

In view of the heavy health and economic burden of AD in the USA, in the past two decades, the National Institutes of Health has increased its research budget for AD. The federal investment has increased rapidly to about 7 times more than that of fiscal 2012, up to 3.8 billion US dollars [66]. Thanks to strong financial support, significant progress has been made in AD research in the USA. The European Union's Horizon 2020 (H2020), which was officially launched in early 2014, has listed dementia as a major challenge in population change and health, and increased investment in research and innovation.

One difficulty is still being able to make early diagnostics for AD and allow early drug intervention when available. The WHO ICOPE program [63] is designed to follow intrinsic capacities (IC) digitally, including memory in an integrated care way. Once memory loss is detected by the ICOPE step 1, with the ICOPE digital monitor tool, steps 2 and 3 will allow for an early diagnosis if needed [64]. ICOPE is also available in Chinese [65]. Digital ICOPE monitor tool associated with plasma biomarkers (e.g., pTau 217) will help to pave the way for early diagnosis of AD and to refer patients to a specialized memory clinic for further assessment and treatment.

Since dementia is a progressive disease, it takes a much longer time and more study participants to perform a clinical trial in AD than in other diseases. To expedite the development of new therapeutic drugs, the US FDA recently decided to use biomarkers that have a reasonably predictive value as a surrogate for accelerated approval of DMT treatment for AD. In the case of anti-Aβ antibody trials, if the reduction of Aβ was used as a surrogate, the length of the trial could be shortened by three times to six months and the recruitment of study participants could be reduced to a few hundred instead of thousands. This will certainly help to make more DMT treatment for AD patients in need.

6. Conclusions

It is urgent to have specific and easily accessible biomarkers for the early diagnosis of AD, which is crucial for timely intervention, since drugs become available now to slow disease progression and to improve the overall quality of life. To address this challenge, researchers are exploring innovative approaches, including advanced neuroimaging techniques, biomarker identification, and cognitive assessments, etc. [67–69] Integrating advanced technologies and precision medicine holds the promise of improving early diagnosis, but careful scientific validation and ethical considerations are essential to ensure safe, reliable, and equitable implementation of early diagnostic tools and interventions.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

Jiong Shi, Yong Shen, and Bruno Vellas designed this article. Jacques Touchon, Lefkos T Middleton, Mercé Boada Rovira and Robert Vassar participated in the discussion of the article's structure, information gathering, and revisions of the manuscript. Jiong Shi wrote the draft of the manuscript. All authors have reviewed and approved the final version of the article.

References

[1] Wang Q, Gao F, Dai LN, et al. Clinical research investigating Alzheimer's disease in China: current status and future perspectives toward prevention. J Prev Alzheimers Dis 2022;9:532–41.
[2] Rajan KB, Weuve J, Barnes LL, et al. Population estimate of people with clinical Alzheimer's disease and mild cognitive impairment in the United States (2020–2060). Alzheimers Dement 2021;17:1966–75.
[3] Jia L, Du Y, Chu L, et al. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: A cross-sectional study. Lancet Public Health 2020;5:e661–71.
[4] Hampel H, Vergallo A, Iwatsubo T, et al. Evaluation of major national dementia policies and health-care system preparedness for early medical action and implementation. Alzheimers Dement 2022;18:1993–2002.
[5] 2021 Alzheimer's disease facts and figures. Alzheimers Dement 2021;17:327–406.
[6] Alzheimer Europe (2019). Dementia in Europe Yearbook 2019 - Estimating the prevalence of dementia in Europe 2019. https://www.alzheimer-europe.org/sites/default/files/alzheimer_europe_dementia_in_europe_yearbook_2019.pdf (Accessed Sep 20, 2024)
[7] Collaborators GBD. Global mortality from dementia: Application of a new method and results from the Global Burden of Disease Study 2019. Alzheimers Dement 2021;7:e12200.
[8] Ikeda S, Mimura M, Ikeda M, et al. Economic burden of Alzheimer's disease dementia in Japan. J Alzheimers Dis 2021;81:309–19.
[9] Jia L, Quan M, Fu Y, et al. Dementia in China: epidemiology, clinical management, and research advances. Lancet Neurol 2020;19:81–92.
[10] Koyama T, Sasaki M, Hagiya H, et al. Place of death trends among patients with dementia in Japan: A population-based observational study. Sci Rep 2019;9:20235.
[11] Nakahori N, Sekine M, Yamada M, et al. Future projections of the prevalence of dementia in Japan: Results from the Toyama dementia survey. BMC Geriatr 2021;21:602.
[12] Robinson L, Tang E, Taylor JP. Dementia: Timely diagnosis and early intervention. BMJ 2015;350:h3029.
[13] McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology 1984;34:939–44.
[14] Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734–46.
[15] Jack Jr CR, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:257–62.
[16] Jack Jr CR, Bennett DA, Blennow K, et al. NIA-AA research framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535–62.
[17] Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. Alzheimers Dement 2018;14:981–8.
[18] Hanseeuw BJ, Betensky RA, Jacobs HIL, et al. Association of amyloid and Tau with cognition in preclinical Alzheimer disease: A longitudinal study. JAMA Neurol 2019;76:915–24.
[19] Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: Recommendations of the International working group. Lancet Neurol 2021;20:484–96.

[20] Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: Towards clinical implementation. Lancet Neurol 2022;21:66–77.
[21] Bruandet A, Richard F, Bombois S, et al. Cognitive decline and survival in Alzheimer's disease according to education level. Dement Geriatr Cogn Disord 2008;25:74–80.
[22] Yang XY, Hou XH, Bi YL, et al. Anaemia and cerebrospinal fluid biomarkers of Alzheimer's pathology in cognitively normal elders: The CABLE study. BMC Neurol 2021;21:454.
[23] Jiao B, Liu H, Guo L, et al. Performance of plasma amyloid beta, total Tau, and neurofilament light chain in the identification of probable Alzheimer's disease in South China. Front Aging Neurosci 2021;13:749649.
[24] Gao F, Lv X, Dai L, et al. A combination model of AD biomarkers revealed by machine learning precisely predicts Alzheimer's dementia: China aging and neurodegenerative initiative (CANDI) study. Alzheimers Dement 2022;19:749–60.
[25] Gao F, Dai L, Wang Q, Liu C, et al. China Aging and Neurodegenerative Initiative (CANDI) Consortium. blood-based biomarkers for Alzheimer's disease: A multicenter-based cross-sectional and longitudinal study in China. Sci Bull 2023;30(68):1800–8.
[26] Wu X, Xiao Z, Yi J, et al. Development of a plasma biomarker diagnostic model incorporating ultrasensitive digital immunoassay as a screening strategy for Alzheimer disease in a Chinese population. Clin Chem 2021;67:1628–39.
[27] Xiao Z, Wu X, Wu W, et al. Plasma biomarker profiles and the correlation with cognitive function across the clinical spectrum of Alzheimer's disease. Alzheimers Res Ther 2021;13:123.
[28] Shen Y, Wang H, Sun Q, et al. Increased plasma beta-secretase 1 may predict conversion to Alzheimer's disease dementia in individuals with mild cognitive impairment. Biol Psychiatry 2018;83:447–55.
[29] Liu YH, Wang J, Li QX, et al. Association of naturally occurring antibodies to beta-amyloid with cognitive decline and cerebral amyloidosis in Alzheimer's disease. Sci Adv 2021;7:eabb0457.
[30] Jiang Y, Zhou X, Ip FC, et al. Large-scale plasma proteomic profiling identifies a high-performance biomarker panel for Alzheimer's disease screening and staging. Alzheimers Dement 2022;18:88–102.
[31] Alegret M, Sotolongo-Grau O, de Antonio EE, et al. Automatized FACEmemory® scoring is related to Alzheimer's disease phenotype and biomarkers in early-onset mild cognitive impairment: The BIOFACE cohort. Alzheimers Res Ther 2022;14:43.
[32] Serrano-Pozo A, Frosch MP, Masliah E, et al. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 2011;1:a006189.
[33] Jia L, Qiu Q, Zhang H, et al. Concordance between the assessment of Aβ42, T-tau, and P-T181-tau in peripheral blood neuronal-derived exosomes and cerebrospinal fluid. Alzheimers Dement 2019;15:1071–80.
[34] Karran E, De Strooper B. The amyloid hypothesis in Alzheimer disease: New insights from new therapeutics. Nat Rev Drug Discov 2022;21:306–18.
[35] Shi J, Sabbagh MN, Vellas B. Alzheimer's disease beyond amyloid: strategies for future therapeutic interventions. BMJ 2020;371:m3684.
[36] Honig LS, Vellas B, Woodward M, et al. Trial of Solanezumab for mild dementia due to Alzheimer's disease. N Engl J Med 2018;378:321–30.
[37] Bateman RJ, Cummings J, Schobel S, et al. Gantenerumab: An anti-amyloid monoclonal antibody with potential disease-modifying effects in early Alzheimer's disease. Alzheimers Res Ther 2022;14:178.
[38] Kuller LH, Lopez OL. ENGAGE and EMERGE: Truth and consequences? Alzheimers Dement 2021;17:692–5.
[39] van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med 2023;388:9–21.
[40] Company ELa. Lilly's Donanemab significantly slowed cognitive and functional decline in phase 3 study of early Alzheimer's disease. https://investor.lilly.com/news-releases/news-release-details/lillys-donanemab-significantly-slowed-cognitive-and-functional.
[41] Shanghai Hengrui Pharmaceutical Co. Ltd. A Phase Ib, Randomized, double-blind, placebo-controlled, multiple-ascending dose study to evaluate the safety, tolerability and pharmacodynamics of intravenous administration of SHR-1707 in patients with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease. https://clinicaltrials.gov/study/NCT05681819.
[42] Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: Appropriate use recommendations. J Prev Alzheimers Dis 2023;10:362–77.
[43] Park B. Aducanumab Significantly Reduces Tau Pathology, Clinical Decline in Alzheimer Disease [online]. https://www.empr.com/home/news/aducanumab-significantly-reduces-tau-pathology-clinical-decline-in-alzheimer-disease/(Accessed Sep 20, 2024).
[44] Eli Lilly and Co. Status of Eli Lilly's new Alzheimer's drug: Donanemab. https://www.dementiacarecentral.com/aboutdementia/treating/donanemab.
[45] Shcherbinin S, Evans CD, Lu M, et al. Association of amyloid reduction after Donanemab treatment with Tau pathology and clinical outcomes: The TRAILBLAZER-ALZ randomized clinical trial. JAMA Neurol 2022;79:1015–24.
[46] Li Q, Pan W, Zhou J, et al. Targeting protein aggregation for the treatment of neurodegenerative diseases. Med Plus 2024;1:100005.
[47] Dam T, Boxer AL, Golbe LI, et al. Safety and efficacy of anti-tau monoclonal antibody gosuranemab in progressive supranuclear palsy: A phase 2, randomized, placebo-controlled trial. Nat Med 2021;27:1451–7.
[48] Hoglinger GU, Litvan I, Mendonca N, et al. Safety and efficacy of tilavonemab in progressive supranuclear palsy: A phase 2, randomised, placebo-controlled trial. Lancet Neurol 2021;20:182–92.
[49] Florian H, Wang D, Arnold SE, et al. Tilavonemab in early Alzheimer's disease: Results from a phase 2, randomized, double-blind study. Brain 2023;146:2275–84.
[50] Tsai RM, Miller Z, Koestler M, et al. Reactions to multiple ascending doses of the microtubule stabilizer TPI-287 in patients with Alzheimer disease, progressive supranuclear palsy, and corticobasal syndrome: A randomized clinical trial. JAMA Neurol 2020;77:215–24.
[51] Prasanth MI, Malar DS, Tencomnao T, et al. The emerging role of the sigma-1 receptor in autophagy: Hand-in-hand targets for the treatment of Alzheimer's. Expert Opin Ther Targets 2021;25:401–14.
[52] Lahmy V, Meunier J, Malmstrom S, et al. Blockade of Tau hyperphosphorylation and $A\beta_{1-42}$ generation by the aminotetrahydrofuran derivative ANAVEX2-73, a mixed muscarinic and σ_1 receptor agonist, in a nontransgenic mouse model of Alzheimer's disease. Neuropsychopharmacology 2013;38:1706–23.
[53] Mummery CJ, Borjesson-Hanson A, Blackburn DJ, et al. Tau-targeting antisense oligonucleotide MAPT(Rx) in mild Alzheimer's disease: A phase 1b, randomized, placebo-controlled trial. Nat Med 2023;29:1437–47.
[54] Jung H, Lee SY, Lim S, et al. Anti-inflammatory clearance of amyloid-beta by a chimeric Gas6 fusion protein. Nat Med 2022;28:1802–12.
[55] Pontecorvo MJ, Lu M, Burnham SC, et al. Association of Donanemab treatment with exploratory plasma biomarkers in early symptomatic Alzheimer disease: A secondary analysis of the TRAILBLAZER-ALZ randomized clinical trial. JAMA Neurol 2022;79:1250–9.
[56] Novartis Pharmaceuticals. Exploratory pLatform trial on anti-inflammatory agents in Alzheimer's disease (EXPLAIN-AD): A randomized, placebo-controlled, multicenter platform study to evaluate the efficacy, safety, tolerability and pharmacokinetics of various anti-inflammatory agents in patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease. https://clinicaltrials.gov/ct2/show/NCT04795466 (Accessed Sep 20, 2024)
[57] . Inmune Bio I, Inc. Phase 1b open-label, dose-identification study of XPro1595 in patients with Alzheimer's disease and biomarkers of inflammation 2024;20. , https://clinicaltrials.gov/ct2/show/NCT03943264.
[58] Sun P, Yue H, Xing Q, et al. Compound AD16 reduces amyloid plaque deposition and modifies microglia in a transgenic mouse model of Alzheimer's disease. ACS Pharmacol Transl Sci 2020;3:1100–10.
[59] Shuai Y, Lu B, Hu Y, et al. Forgetting is regulated through Rac activity in Drosophila. Cell 2010;140:579–89.
[60] Beijing Joekai Biotechnology LLC. A phase IIa, double-blind, randomized, placebo-controlled, multicenter study to evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of 50561 in patients with mild or moderate Alzheimer's disease. https://clinicaltrials.gov/ct2/show/NCT05811442.
[61] Wang X, Sun G, Feng T, et al. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. Cell Res 2019;29:787–803.
[62] Green Valley (Shanghai) Pharmaceuticals Co. Ltd. A clinical study to evaluate the long-term efficacy and safety of sodium oligomannate capsules (GV-971) Sep;20:2024. https://clinicaltrials.gov/study/NCT05181475 (Accessed Sep 20, 2024).
[63] Green Valley (Shanghai) Pharmaceuticals Co Ltd. A clinical study to evaluate the long-term safety sodium oligomannate capsules (GV-971) 2024;20. , https://clinicaltrials.gov/study/NCT05058040.
[64] Green Valley (Shanghai) Pharmaceuticals Co Ltd. An efficacy and safety study of sodium oligomannate (GV-971) for the treatment of Alzheimer's disease. 2023 2024;20. , https://clinicaltrials.gov/study/NCT05908695.
[65] World Health Organization. Dementia. https://www.who.int/news-room/fact-sheets/detail/dementia.
[66] Alzheimer's Impact Movement. Alzheimer's and related dementia research funding at the NIH. https://www.alzimpact.org/appropriations(Accessed Sep 20, 2024).
[67] Liu W, Gauthier S, Jia J. Alzheimer's disease: current status and perspective. Sci Bull 2022;67:2494–7.
[68] Liu X, Gao T, Lu T, et al. China brain project: from bench to bedside. Sci Bull 2023;68:444–7.
[69] Lu J, Li Z, Gitler AD, et al. Drugging "undruggable" neurodegenerative disease targets with small molecules. Sci Bull 2023;68:1715–8.

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